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CT-011, ANTI PD-1 ANTIBODY, ENHANCES EX-VIVO T CELL RESPONSES TO AUTOLOGOUS DENDRITIC/MYELOMA FUSION VACCINE DEVELOPED FOR THE TREATMENT OF MULTIPLE MYELOMA

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We have developed a cancer vaccine in which autologous myeloma cells are fused with dendritic cells (DCs) resulting in the presentation of tumor antigens in the context of DC mediated costimulation. In animal models, vaccination with fusion cells results in eradication of established tumor, and in clinical trials, both immunologic and clinical responses have been observed. However, response to vaccination may be muted by inhibitory signals such as the PD1/PDL1 pathway which blunt activated T cell responses. In this study, we evaluated expression of PD1 on T cells derived from patients with multiple myeloma (MM), and PDL1 expression on primary myeloma cells and DC/MM fusions. We evaluated the effect of PD-1 blockade on T cell response to DC/MM fusion cell vaccination in vitro. Tumor cells were obtained from bone marrow aspirates of MM patients. Nonadherent peripheral blood mononuclear cells (PBMCs) obtained from patients with MM and normal volunteers were cultured in RPMI supplemented with 10U/ml IL-2, and expression of PD-1 on CD4 + T cells was assessed by flow cytometry. DCs were generated from adherent PBMCs cultured with rhIL-4, GM-CSF and TNFα and fused with MM cells by coculture in 50% solution of PEG. T cells were stimulated by DC/MM fusions in the presence or absence of PD-1 blockade. We demonstrate that PD-1 expression is markedly upregulated on T cells in patients with advanced MM. As compared to a control population in which mean levels of PD-1 expression was 6% (n = 7), mean expression in patients with MM was 20% (n = 9). Mean expression of PDL-1 was 66% on patient derived MM cells (n = 3) and > 90% on DC/MM fusions (n = 2), which potentially provides an inhibitory signal dampening fusion mediated immunologic response. We examined the effect of PD-1 blockade on T cell response to DC/MM fusions ex vivo. Enhanced fusion mediated stimulation of T cells was noted in the presence of anti-PD-1, resulting in a greater than 5 fold increase in T cell proliferation. Interferon gamma secretion by CD4 + T cells in response to stimulation by DC/MM fusions increased from 4% to 11% in the presence of PD1 blockade, while IL-10 secretion decreased from 6.5% to 3.5%. In summary, we demonstrate that PD-1 expression is increased in T cells of MM patients, and PD-1 blockade enhances activated T cell responses following stimulation with a DC/MM fusion vaccine. A clinical trial in which MM patients are treated with DC/MM fusions in conjunction with anti-PD1 is planned.

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CYTOKINE LEVELS IN PATIENTS WITH PLASMA CELL DISORDERS (PCD) UNDERGOING PERIPHERAL BLOOD STEM CELL TRANSPLANT (PBSCT)

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Background: We reported increased rates of engraftment syndrome (ES) and associated morbidity in POEMS patients undergoing PBSCT. The condition is successfully treated with early institution of corticosteroids. We postulated that the high rates of ES in these patients relates to their pre-existing aberrant cytokine milieu.
Methods: To test this hypothesis, we prospectively collected plasma samples from patients undergoing PBSCT on day -2, 1, 4, 7, 10, 17 and 20. Charts were abstracted independent of knowledge of cytokine information. Cytokine levels were run using BioSource Multiplex Bead Immunoassays Platform (Human cytokine 30-PLEX)–30 different human cytokines, chemokines and growth factors. ES was defined according to published criteria by Maiolino *et al.* (BMT 2003) allowing for more liberal time relative to neutrophil engraftment.
Results: A total of 18 patients were sampled: 9 POEMS, 4 multiple myeloma (MM), and 5 amyloidosis (AL). Baseline characteristics are summarized in Table 1. POEMS patients had higher median pre-transplant levels of IL-4 (14.9 v 2.9 pg/mL p=0.03), IL-10 (14.3 v 10.7 pg/mL, p = 0.004), EGF (31.7 v 0.0 pg/mL, p = 0.001), and IFN-a (39.4 v 0.0 pg/mL, p = 0.01) than the patients with the other PCDs. IP-10 was lower in POEMS patients (21.7 vs 43.1 pg/mL p = 0.02). Day -2 plasma VEGF level was not significantly higher in POEMS patients presumably since 67% of them received chemotherapy prior to PBSCT. Five patients developed ES – 2 POEMS, 2 AL and 1 MM – at a median of 10 days (range 8-13). Lower levels of IL-1Ra and IL-15 post-transplant were associated with increased risk of ES, $p < 0.05$. Delayed engraftment of neutrophils correlated with higher levels of IL-13 and EGF pre- and post-transplant.
Conclusion: These data are provocative in that they demonstrate that prior to transplantation, the cytokine milieu differs between POEMS patients and those with other PCDs, that EGF and IL-13 may predict for delayed engraftment, and that lower levels of IL-1Ra and IL-15 may be associated with increased risk of ES. Larger numbers of patients will be required to validate our findings.

Patient Characteristics

	POEMS (n = 9)	non-POEMS (n = 9)
	%	%
Age in years, median (range)	52 (35-68)	62 (50-70)
Gender, M	44	89
Caucasian race	67	89
KPS, median (range)	70 (50-80)	90 (70-100)
Polyneuropathy	100	0
Organomegaly	78	11
Endocrinopathy	100	11
Skin Involvement	78	0
Extravascular fluid overload	100	44
Sclerotic bone lesions	67	0
Castleman's dz	56	0
Splenomegaly	56	0
Papilledema	22	0
Prior treatments, median (range)	2 (1-4)	1 (0-7)
Chemo prior to transplant	67	78
Conditioning, Mel 200	67	78
Mobilization, G alone	89	67
CD34 infused, (x106/kg), median (range)	3.88 (2.9-14.6)	4.93 (3.45-7.49)
Engraftment syndrome	22	33
Engraftment*, days, median (range)		
ANC > 500/uL	15 (13-19)	13 (12-15)
Platelets > 20/uL	11 (0-20)	13 (11-20)
Platelets > 50/uL	14 (12-27)	15 (12-25)

*two non-POEMS patients died prior to platelet engraftment

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A NOVEL HAPLO-IDENTICAL ADOPTIVE CTL THERAPY AS TREATMENT FOR EBV-ASSOCIATED LYMPHOMA AFTER STEM CELL TRANSPLANTATION

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Epstein-Barr virus (EBV) related malignancies such as post-transplant lymphoproliferative disease (PTLD) are severe complications after allogeneic stem cell transplantation (SCT) and solid organ transplantation. In immune suppressed transplant recipients the activity of EBV-specific CTLs are often decreased or absent which leads to an increased risk of developing PTLD. If primary treatment modalities of PTLD fail, the most efficient way of treating the malignancy is adopting EBV-specific CTLs from the donor or, more recently, third-party donors. This is however both time-consuming and expensive and often it is too late to administer cells to the patient.

We have for the first time, using a rapid isolation protocol of EBV-specific T cells, treated and cured a patient suffering from PTLD with multiple associated tissue lesions, using her haplo-identical mother as a donor. This treatment approach paves way for a new possibility to within days treat patients with life-threatening EBV-associated malignancies.

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ALLOGENEIC STEM CELL TRANSPLANTATION WITH REDUCED INTENSITY CONDITIONING AS TREATMENT FOR MATURE T-CELL LYMPHOMAS

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Background: For aggressive lymphomas a T-cell phenotype confers a poor prognosis. Current therapeutic strategies for T-cell non-Hodgkin lymphoma (NHL) are poorly defined. Allogeneic stem cell transplantation (Allo-HCT) is a potentially curative option but associated with high non-relapse mortality (NRM). Reduced intensity conditioning (RIC) is designed to minimize NRM while using the benefits of the graft-versus-lymphoma effect. Here we report retrospective analysis of patients with T-cell NHL who underwent Allo-HCT with RIC using fludarabine and melphalan.

Patients and Methods: A consecutive case-series of 27 patients with mature T-cell NHL were included. All patients underwent RIC with fludarabine and melphalan. Histologies included: PTCL NOS (n = 5); AILD (n = 3); ALCL (n = 2; both alk+); rare histologies (n = 6) (NK/T cell, enteropathy type, hepatosplenic); and cutaneous T-cell lymphomas (n = 11). Most patients (n = 18, 67%) had advanced disease at the time of transplant: relapse/induction failure = 17, progression = 1. The rest of the patients were in CR1 = 1, CR2 = 5, PR = 3. The median age was 50 years (range: 19-68), 74% were male (n = 20). The time from diagnosis to transplant for majority of the patients (n = 20, 74%) was more than one year. The median number of prior regimens was 4 (range: 1-9); one patient had a prior autologous transplant. All patients received stem cells, 56% from HLA-matched sibling and 44% from matched unrelated donor. 18 patients (67%) received GVHD prophylaxis with sirolimus/tacrolimus, while 9 patients (33%) received cyclosporine/cellcept based prophylaxis.

Results: The median follow-up for the 16 (59%) surviving patients was 24.2 months (range: 5.6-95.3). Day 100 mortality was 22% (n = 6). There were a total of 11 deaths; 5 from disease progression/relapse and 6 from non-relapse causes. 13 patients (48%) experienced acute GVHD: grade I = 4, grade II = 5, grade IV = 4. Among the 17 patients who are evaluable for chronic GVHD, 11 (63%) patients developed an extensive GVHD. The 2-year probability of overall (OS) and disease-free (DFS) survival were 55% (95%CI: 43-65%) and 43% (95%CI: 34-52%) respectively. The relapse/progression and NRM rates at 2 years were 37% (95%CI: 26-52%) and 28% (95%CI: 16-46%) respectively.

Conclusion: The overall results show that good long term survival rates and disease control can be achieved with acceptable non-relapse mortality in patients with mature T-cell lymphomas using reduced intensity conditioning.

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THE IMPORTANCE OF TIMING OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN PATIENTS WITH T-CELL LYMPHOMAS (T-NHL)

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Patients (pts) with T-NHL have a poor prognosis with standard chemotherapy. HSCT have been used in their management but the most appropriate time for HSCT is not clear. We previously reported the poor outcome of pts with ALK negative (anaplastic lymphoma kinase) anaplastic large cell lymphoma (ALCL) having HSCT after first recurrence (Zamkoff et al, BMT 33:635-8,2004). To further investigate outcomes of pts transplanted for T-NHL, we retrospectively analyzed 33 pts undergoing autologous HSCT from August 2000 to July 2009. 23 were male, 10 female; median age was 53.2 (29 -73) years at time of HSCT. Subtypes of T-NHL included Alk negative ALCL (9) and Alk positive ALCL (1); peripheral T-Cell (PTCL), not otherwise specified (11); Angioimmunoblastic (AILT) (9); Nasal NK/T (2) and cutaneous T-cell (CTCL) (1). 6 pts were in their first complete remission (CR1), 1 in CR1 unconfirmed (CRU1), 10 in first partial remission (PR1), 9 in first relapse (Rel1) with 8 sensitive and 1 refractory, 3 in CR2, and 4 in second or later sensitive relapse (Rel2+). Preparative regimens for HSCT included Cy/TBI (13) or Cy/etoposide/TBI (9), Bu/Cy (6), CBV (4), and BEAM (1).

Among the 12 pts in CR1/CRU1 or PR1 < 200 days from diagnosis (Group 1), there were 2 with Alk negative ALCL, 5 PTCL, 4 AILT, and 1 Nasal NK/T. Among the 21 pts (Group 2), there were 7 with Alk negative ALCL, 1 Alk positve ALCL, 6 PTCL, 5 AILT, 1 Nasal NK/T, and 1 CTCL.

With a median follow-up of 17.6 (0.4-84.0) months post HSCT, the overall survival (OS) is estimated to be 52% and progression free survival (PFS) is 45%. 16 pts have expired. Causes of death include relapse (12), transplant related mortality (1), second malignancy (1), and unknown (2) since no MD follow-up records available.

Among the 17 surviving pts, 10 were among the 12 pts in Group 1. For this group, the OS is 83% with a PFS of 75% at a median follow-up of 18.6 (0.7-60.5) months. 7 additional pts survive among the Group 2 pts; their OS is 33% and PFS is 29% at a median follow-up of 15.2 (13-84) months. In Group 2, surviving pts include 1 of 3 transplanted in CR2; 6 of 13 transplanted in Rel1 or Rel2+ and 0 of 5 in PR1 transplanted >200 days from diagnosis.

In summary, this data would suggest an improved outcome for HSCT in pts with T-NHL when applied earlier in the course of their disease. Such a strategy should be evaluated in a larger prospective trial of HSCT in CR1/PR1 to evaluate the efficacy and safety across the various subtypes T-NHL.

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PREFERENCE OF PATIENTS AND PHYSICIANS CONCERNING TREATMENT OPTIONS FOR RELAPSED FOLLICULAR LYMPHOMA: A DISCRETE CHOICE EXPERIMENT

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Background: Patients with symptomatic relapsed follicular lymphoma, together with their physicians, must choose between a variety of treatment options. The purpose of this study was to elicit relative preferences for attributes associated with different treatment options amongst lymphoma patients in Alberta, and lymphoma-treating physicians in Canada, using a discrete choice experiment (DCE).

Methods: 180 patients aged 18-65 years and 252 physicians received background information and a questionnaire containing the DCE. Treatment administration, toxicity, average remission length, and cost were the attributes evaluated for four treatment options: standard chemotherapy (CT), radioimmunotherapy (RIT), high-dose chemotherapy and autologous (AUTO) or allogeneic (ALLO) stem cell transplantation. In a series of multiple choice questions, respondents were asked to choose between two unlabeled treatment options, described according to the attributes where the attribute levels were different for each option. The DCE was analyzed using a random effects logit model. Marginal rates of substitution calculated from regression coefficients provided information about preference for the treatment attributes.

Results: 81 patients (45%) and 48 physicians (19%) completed the questionnaire. Responding patients had a mean age of 54.7 years and were on average 4.4 years from initial diagnosis. 93% of patients